

**REMARKS**

Claims 1-103 are pending in the subject application. Claims 1-34 and 53-103 have been withdrawn from consideration as being directed to a non-elected invention. Applicants' reserve the right to pursue prosecution of these non-elected claims in a later filed application claiming priority to the subject application. Accordingly, claims 35-52 are currently under examination. Claim 35 has been amended. Support for the amendments can be found throughout the application as filed. Support for the amendment to claim 35 reciting an adapter sequences that differs from the target sequences can be found at, for example, paragraph [0071] (page 17, line 29 through page 18, line 2). Support for the amendment to claim 35 reciting relative amounts of the first target sequence relative to the second target sequence can be found at, for example, [408] and [094]. Claim 48 has been amended to correct an obvious informality. Accordingly, the amendments do not raise any issues of new matter and entry thereof is respectfully requested. Applicant has reviewed the rejections set forth in the Office Action mailed July 19, 2006, and respectfully traverse all grounds for the reasons that follow.

**Double Patenting**

Claims 35-52 stand provisionally rejected under the judicially-created doctrine of obvious-type double patenting as allegedly unpatentable over claims 5, 6, 11 and 13-30 of copending application serial no. 10/194,958. Claims 35, 39, 41-44, 47 and 49 stand rejected allegedly for obvious-type double patenting over claims 1-2, 10, 18, 20-24, 32, 39-40, 42-46, 54 and 64-66 of copending application 10/864,935. The Office alleges that, although the conflicting claims are not identical, they are obvious over each because they are drawn to methods containing similar steps. Applicants respectfully defer responding to this provisional rejection until there is an indication of allowable subject matter one or both of the allegedly conflicting application.

**Rejections Under 35 U.S.C. § 112**

Claims 35-52 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly because it is unclear whether the first and second amplicons are quantified separately. Claim 48 stands

rejected allegedly because the phrase “said plurality of probes comprises at least 8, 96, 192, 384, 1152, or 1536” is unclear.

The requirement for precision in claiming is set forth in the second paragraph of § 112. The statute is satisfied if a person skilled in the field of the invention would reasonably understand the claim when read in the context of the specification. *Marley Moldings Limited v. Mikron Industries, Inc.*, Case No.04-1441, slip op. at 5 (Fed. Cir. August 8, 2005) citing *Union Pac. Res. Co. v. Chesapeake Energy Corp.*, 236 F.3d 684, 692 (Fed. Cir. 2001) (the definiteness requirement of §112, second paragraph “focuses on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the rest of the specification”).

Applicants submit that the claims are clear as written. Claim 35 is directed to a method of detecting relative amounts of two or more target sequences. Initially, with respect to the Office’s characterization that the claimed detection method quantitates amplicons, Applicants’ respectfully draw the Offices attention to the preamble which recites “detecting the relative amounts of two or more target sequences.” Detection of relative amounts using the claimed method of the invention can be employed in ether a quantitative or qualitative fashion as described throughout the application. Nevertheless, claim 35 has been amended to explicitly recite that the reference to relative amounts of first and second amplicons is indicative of the relative amounts of the claimed first target sequence with respect to the second target sequence. In light of this amendment, Applicants submit that the rejection is now moot and its withdrawal is respectfully requested.

With respect to claim 48, and its recitation of the number probes within the claimed plurality. Claim 48 depends from claim 47, which depends from base claim 35 and recites contacting a plurality of pairs of ligation probes with a plurality of target sequences to form a plurality of ligation complexes. Claim 48 has been amended to further conform to the term used in claim 47 and now recites that the claimed number of probes refers to “pairs of probes.” Accordingly, this ground of rejection is now moot in light of the amendment to correct this obvious informality.

**Rejections Under 35 U.S.C. § 103**

Claims 35-42, 45-46 and 49-52 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bhatnagar et al., U.S. Patent No. 5,593,840, in view of Morris et al., U.S. Patent No. 6,017,738 (cited as Phillip et al.). The Office alleges that Bhatnagar et al. describe a process for amplifying a nucleic acid sequence for detection of a point mutation which extends and ligates first and second primers followed by amplification of the product. The Office concedes that Bhatnagar et al. do not disclose linear amplification, a first or second universal priming site, an adapter sequence-containing probe or determining a relative amount of first and second amplicons. The Office alleges linear amplification is accomplished through product extension using a third primer and that Bhatnagar's extension and/or ligation primers correspond to the claimed universal primers and/or adapter sequences because these elements lack physical features other than binding to a primer for amplification or hybridization. Morris et al. is alleged to describe a method using a solid phase amplification method which incorporates a label using RNA transcription. The Office concludes that it would have been obvious to apply the method of Bhatnagar et al. to determine the relative amount of first and second amplicons allegedly because Morris et al. describe that incorporation of label into amplified nucleic acid sequences allows detection and quantification.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 U.S.P.Q. 580 (C.C.P.A. 1974); M.P.E.P. §2143.03. Applicants claim first and second pairs of ligation probes to first and second target sequences where each probe pair has an adapter sequence. As described further below, this sequence is physically different and absent from any description of the primers in Bhatnagar et al..

Applicants respectfully point out that paragraph [0072] recites distinctions other than hybridization characterizations. Moreover, paragraph [0071] explicitly teaches that adapter sequences differ from target sequences when it describes:

In a preferred embodiment, one of the probes further comprises an adapter sequence, (sometimes referred to in the art as "zip codes" or "bar codes"). Adapters facilitate immobilization of probes to allow the use of "universal arrays". That is, arrays . . . are generated that contain capture probes that are **not**

target specific, but rather specific to individual (preferably) artificial adapter sequences.

*Id.* (emphasis added).

The above paragraph clearly teaches features of adapter sequences other than hybridization characteristics that distinguish adapters from target sequences. Applicant's have amended claim 35 above to explicitly include the definition of the term "adapter sequence" as differing from the claimed first and second target sequences.

Because both paragraph [0072] and it's preceding paragraph [0071] describe adapter sequences as being distinct from the target sequences they cannot satisfy the primers of Bhatnagar et al. as relied on by the Office. For example, Bhatnagar et al. describe the hybridization of complementary primers to a target sequence, extension of the primers followed by ligation. The primers described by Bhatnagar et al. are characterized as being substantially complementary to the target sequence (col. 9, lines 56-60, and Figure 3). Applicants' have found no teaching in Bhatnagar et al. of primer regions complementary to something other than a target sequence. In this respect, Bhatnagar et al. describe that the target nucleic acid is hybridized to two primers where:

The first primer is substantially complementary to the 5' end of the target nucleic acid sequence and the second primer is substantially complementary to the 3' end of the target nucleic acid.

*Id.*

Accordingly, Bhatnagar et al. describe at most two primers where each is substantially complementary to the target nucleic acid sequence. In contrast, the claimed invention is directed to hybridizing first and second pairs of ligation probes with first and second target sequences where each pair of ligation probes contain an adapter sequence that differs from the first and second target sequences. Therefore, at least one of the probes within a claimed pair of ligation probes includes an adapter sequence. The adapter sequence differs from the target sequence and is, therefore, not taught or suggested by the substantially complementary target sequence primers described by Bhatnagar et al.

Accordingly, Bhatnagar et al. fails to teach or suggest this element of the claimed invention. Morris et al., cited for allegedly describing detection of nucleic acids through label incorporation, similarly fails to describe adapter sequences or teach, suggest or motivate one skilled in the art to arrive at the claimed invention from Bhatnagar et al. because Morris et al. is directed to incorporation of labels for detection of PCR products. Absent some teaching, suggestion or motivation in Bhatnagar et al. and Morris et al. that would lead one skilled in the art to arrive at the claimed adapter sequences that differ from target sequences the cited combination cannot render the claimed invention obvious because all claimed elements have neither been taught or suggested. Therefore, withdrawal of this ground of rejection is respectfully requested.

Dependent claims 43 and 44 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bhatnagar et al. in view of Morris et al. as applied above and further in view of Barany et al., U.S. Patent No. 6,027,889. The Office concedes that Bhatnagar et al. do not describe immobilizing target nucleic acid sequences to a solid support. Barany et al. is alleged to describe detection of nucleic acid sequence differences using coupled ligase detection and PCR in which the amplified products are immobilized to an addressable array by capture probes complementary to nucleotide sequences across the ligation junction. The Office concludes that it would have been obvious to apply the addressable array of Barany et al. to the method of Bhatnagar et al. for determining relative amounts of amplicons allegedly because Barany et al. that the use of an addressable array allows determining the presence of one or more target nucleotide sequences in a sample.

Claims 43 and 44 depend from and contain all elements of base claim 35. Barany et al. is cited for allegedly describing immobilization to an addressable array by capture probes. Because base claim 35 is unobvious over the combination of Bhatnagar et al. in view of Morris et al., absent some teaching, suggestion or motivation in Barany et al. to combine the method of Bhatnagar et al. with the labeling method of Morris et al. for determining relative amounts of first and second amplicons in a method which employs adapter sequences that differ from the target sequences, the cited combination fails to render the claimed invention obvious.

The Office concedes that the capture probes of Barany et al. are complementary to nucleotide sequences across the ligation junction (*citing* col. 24, lines 55-60). This junction is described by Barany et al. to correspond to the target sequence regions (see, for example, col. 24, lines 24-29). Because the ligation junction corresponds to a target-specific sequence, the description of Barany et al. also does not teach or suggest an adaptor sequence that differs from a target sequence as claimed and, accordingly, fails to provide the requisite teaching, suggestion or motivation for one to arrive at all elements of the claimed invention from the cited combination of Bhatnagar et al., Morris et al. and Barany et al. Therefore, withdrawal of this ground of rejection is respectfully requested.

Dependent claims 47 and 48 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bhatnagar et al., in view of Morris et al. as applied above and further in view of Akhavan-Tafti, U.S. Patent No. 5,998,175. The Office concedes that Bhatnagar et al. and Morris et al. do not disclose a plurality of more than two pairs of ligation probes with a plurality of more than two target sequences, but alleges that Akhavan-Tafti describes a method of synthesizing polynucleotides using simultaneous ligation of a set of oligomers onto a template bound primer which inherently describes the use of a plurality of more than two pairs of ligation probes. The Office concludes that it would have been obvious to apply the plurality of pair of ligation probes as claimed allegedly because the method of Akhavan-Tafti can be used to copy DNA or RNA linearly or exponentially.

Claims 47 and 48 depend from and contain all elements of base claim 35. Akhavan-Tafti is cited for allegedly describing more than two pairs of ligation probes and similarly fails to provide the missing teaching, suggestion or motivation from the combination of Bhatnagar et al. and Morris et al. to arrive at the claimed adapters that differ from the target sequences because the synthesis procedure described by Akhavan-Tafti is described as using primers complementary to the template or target sequence (see, for example, col. 4, lines 48-50). Accordingly, the cited combination fails to render the claimed invention obvious and withdrawal of this ground of rejection is respectfully requested.

**CONCLUSION**

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call David Gay.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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